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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P17218/RMC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/GB97/00577	International filing date *(day/month/year)* 03/03/1997	Priority date *(day/month/year)* 01/03/1996
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant THE UNIVERSITY COURT OF THE UNIVERSITY OF ..et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/09/1997	03. 06. 98
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Wieser, M Telephone No. (+49-89) 2399-8434

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International application No. PCT/GB97/00577

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the [illegible] Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,2,4-23	as originally filed			
3,3a	as received on	03/04/1998	with letter of	30/03/1998

Claims, No.:

1-14	as received on	03/04/1998	with letter of	30/03/1998

Drawings, sheets:

1/4-4/4	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12,14
	No:	Claims	13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

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Point V:

1. The New England Journal of Medicine, vol.333, No.18, Nov.1995, pages 1171-1175 (hereinafter referred to as document A) discloses a test for the detection of the genetic basis of the reduced expression of bilirubin UDP-Glucuronosyl-transferase 1 in Gilbert's syndrome. It is shown that the primary genetic factor contributing to Gilbert's syndrome is a 2bp insertion in the TATA box of the 5' promoter region of the gene coding for the enzyme. Document A does not explicitly disclose the use of this test in a method to improve the efficacy of drug trials.

   Thus, the subject-matter of claims 1-12 is novel in the light of the disclosure in document A (Article 33(2) PCT). The same applies to claim 14, referring to the use of specific primers which are not disclosed in the prior art.

   Claim 13, referring to a kit is anticipated by the disclosure in document A (see page 1172, methods) and does not meet the requirements of Article 33(2) PCT.

2. The subject-matter of claims 1-14 is not based on an inventive concept and does not meet the requirements of Article 33(3) PCT.

   The genetic basis of Gilbert's Syndrome, as well as a test for detecting it, is known from document A. The findings made by the authors of document A are acknowledged on page 10, lines 21-29 of the present application.

   The use of this well known test to screen samples of individuals for potential participants in a drug trial, i.e. a trial to test the efficacy of a drug in fighting Gilbert's syndrome, cannot be considered as being based on an inventive concept within the meaning of Article 33(3) PCT. In fact, no drug trial would ever be started by a skilled person without the initial step of selecting individuals from a mixed population who are indeed affected by the disease or syndrome whose response to the drug are to be tested. Any mode of proceeding which departs from this scheme would be highly illogical and counterproductive with regard to the result and evidence provided by said drug trial.

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The specific primers referred to in claim 14, for use in the well known test of document A, do not seem to bring about any surprising result. Thus claim 14 is also not considered to be inventive.

Due to the benign nature of the syndrome and its prevalence in the population it may be more appropriate to consider GS as a normal genetic variant[2] exhibiting a reduced bilirubin glucuronidation capacity (which in certain situations such as fasting, illness or administration of drugs) could precipitate jaundice.

In drug trials where high levels of serum total bilirubin is detected for certain individuals, it is not clear whether this is because the individuals have Gilbert's Syndrome or if it because of an effect of the drug. Whereas presently, results are explained merely by saying that the individuals have Gilbert's Syndrome, it is suspected that in the future, it will be necessary to prove this fact.

Where a jaundiced phenotype is apparent after volunteers have been accepted for a trial and have been subjected to five days of a strict diet, no alcohol and no smoking, the jaundiced appearance giving an indication that the individuals have Gilbert's Syndrome, may cause them to be ruled out of the trials. Therefore, where approximately 250 individuals would be required for phase 1 trials and about 6000 patients for phase 3 trials, unnecessary time and effort would have been spent during the first 5 days of these trials and individuals having Gilbert's Syndrome may be ill effected.

Bosma et al. (New England Journal of Medicine (1995) volume 333 Number 18) reported the genetic basis of Gilbert's syndrome.

The present invention aims to provide a method of improving the efficacy of drug trials in view of the problems mentioned above.

According to the present invention there is provided a method for improving the efficacy of drug trials, the method comprising the step of screening samples from

CLAIMS

1. Use of a test for detecting the genetic basis of Gilbert's Syndrome in a method to improve the efficacy of drug trials, the method comprising screening samples from potential participants for the basis of Gilbert's Syndrome and eliminating or including potential participants in a drug trial in the knowledge of them possessing or not possessing the genetic basis of Gilbert's Syndrome.

2. Use of a test as claimed in claim 1 wherein the method comprise the steps of:

   a) taking a sample from each potential participant in a drug trial,

   b) screening the samples for the genetic basis of Gilbert's Syndrome,

   c) identifying participants having the genetic basis of Gilbert's Syndrome, and

   d) proceeding with drugs trials in the knowledge of participants possessing or not possessing the genetic basis of Gilbert's Syndrome.

3 Use of a test as claimed in claim 1 or 2 wherein the sample is chosen from blood, buccal smear or any other sample containing DNA from the potential participants.

4. Use of a test as claimed in any of the preceding claims further comprising the step of eliminating participants having the genetic basis of Gilbert's

Syndrome from a drugs trial.

5. Use of a test as claimed in any of claims 1 to 3 wherein the method comprises the further step of selecting only participants having genetic basis for Gilbert's Syndrome for a drugs trial.

6. Use of a test as claimed in any of claims 1 to 3 further comprising the step of interpreting the results of the drugs trial in the knowledge that certain participants have Gilbert's Syndrome.

7. Use of a test as claimed in any of the preceding claims wherein the method comprises the steps of:

a) isolating DNA from each sample,

b) amplifying the DNA inner region indicating the genetic basis for Gilbert's Syndrome,

c) isolating amplified DNA fragments, and

d) identifying individuals having the genetic basis of Gilbert's Syndrome.

8. Use of a test as claimed in any of the preceding claims wherein the DNA is amplified using the polymerase chain reaction (PCR) using a radioactively labelled pair of nucleotide primers.

10. Use of a test as claimed in any of claims 7 to 9 wherein the DNA region indicating the genetic basis of Gilbert's Syndrome is the gene encoding UDP-glucuronosyltransferase (UGT).

11. Use of a test as claimed in any of claims 7 to 10

wherein the DNA to be amplified is in an upstream promoter region of the UGT 1*1 exon 1.

12. Use of a test as claimed in any of claims 7 to 11 wherein the DNA to be amplified includes the regions between -35 and -55 nucleotides at the 5' end of UGT 1*1 exon.

13. A kit for screening individuals participation in drug trials, the kit comprising primers for amplifying DNA in the region of the genome indicating the genetic basis of Gilbert's Syndrome.

14. Primers for use of a test as claimed in any of the preceding claims including primer pairs, AB or CD as follows:

A/B(A,5'-AAGTGAACTCCCTGCTACCTT-3',
B,5'-CCACTGGGATCAACAGTATCT-3') or
C/D (C,5'-GTCACGTGACACAGTCAAAC-3';
D 5'-TTTGCTCCTGCCAGAGGTT-3').